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Synthesis of new derivatives of 1-hydroxymethyl and 1-methoxymethyl-dibenzo[e.h]bicyclo[2.2.2]--octane-2,3-dicarboximide with an expected β-adrenolytic activity

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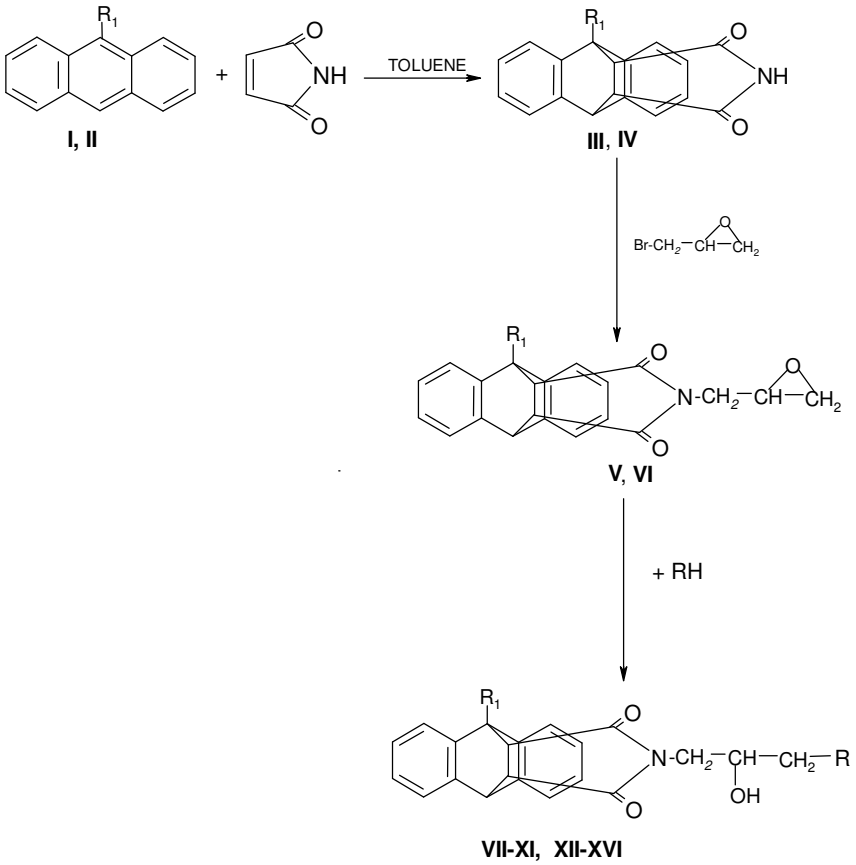
This paper presents the preparation of a number of new derivatives of 1-hydroxymethyl-dibenzo[e.h]bicyclo[2.2.2]-octane-2,3-dicarboximide and 1-methoxymethyldibenzo[e.h]-bicyclo[2.2.2]-octane-2,3-dicarboximide with an expected β-adrenolytic activity.

1. INTRODUCTION

Propranolol, Nadolol and Pindolol (widely used β-blockers) contain 3-isopropylamino-2-hydroxypropyl group – that is associated with their antiarrhytmic and hypotensive activity. As a continuation of our research in new compounds active on the circulation system [1-7], we have decided to synthesise a number of 1-hydroxymethyl and 1-methoxymethyl derivatives of dibenzo[e.h]bicyclo[2.2.2]octane-2,3-dicarboximide.

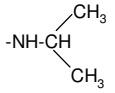
Imides **III** and **IV**, which were obtained in Diels-Alder reaction of 9-antracenemethanol or 9-methoxymethylantracene with maleimide were used as the starting materials. They reacted with 1-bromo-2,3-epoxypropane giving N-(2,3-epoxypropyl)-substituted derivatives **V** and **VI** which were condensed with appropriate amines (Scheme 1).

The structures of new compounds **III-XVI** were confirmed by elemental analysis, IR and ^{1}H NMR (Table 1). The hydrochlorides of compounds **VII, VIII, XII, XIII** will be soon given for pharmacological testing. The results will be published separately.

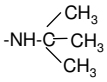


R_1 = -CH_2OH: **I, III, V, VII-XI**
-CH_2-O-CH_3: **II, IV, VI, XII-XVI**

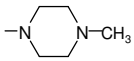
R=



VII, XII



VIII, XIII



IX, XIV

X, XV

XI, XVI

Scheme 1

Tab. 1. Physical, analytical and ^{1}H NMR spectral data of compounds [**I**-**IX**]

Comp. No.	Formula Molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calculated/found %C	%H	%N	^{1}H NMR, δ (ppm) 200 MHz, $CDCl_3$
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
III	$C_{19}H_{15}NO_3$ 305.32	ethyl acetate 266-267	80	74.75 74.63	4.92 5.16	4.59 4.62	^{1}H NMR (DMSO-d_6, 200 MHz): 10.74 (s, 1H, NH), 7.65 (m, 1H, H_{arom}), 7.44-7.08 (m, 7H, H_{arom}), 4.82 (d, J=3.6 Hz, 2H, C$\underline{H_2}$OH), 4.65 (s, 1H, C4-H), 3.22 (d, J=1.2 Hz, 2H, C2-H, C3-H)
IV	$C_{20}H_{17}NO_3$ *0.2 H_2O 319.35	ethyl acetate 260-261	83	74.38 74.41	5.43 5.44	4.34 4.28	^{1}H NMR (DMSO-d_6, 200 MHz): 10.80 (s, 1H, NH), 7.42 (m, 2H, H_{arom}), 7.27 (m, 1H, H_{arom}), 7.15 (m, 5H, H_{arom}), 4.66 (m, 3H, C4-H, -C-C$\underline{H_2}$-O), 3.58 (s, 3H, -OCH_3), 3.19 (m, 2H, C2-H, C3-H)
V	$C_{22}H_{19}NO_4$ 361.38	heptane 172-175	77	73.10 73.29	5.29 5.55	3.87 3.70	7.62 (m, 1H, H_{arom}), 7.40-7.12 (m, 7H, H_{arom}), 5.15 (m, 1H, H_a z CH_2OH), 4.97 (m, 1H, H_b z CH_2OH), 4.77 (m, 1H, C4-H), 3.52-3.28 (m, 5H, C2-H, C3-H, C1'-H, C2'-H), 3.08 (t, 1H, C3'-H), 2.96 (t, 1H, C3'-H).

1	2	3	4	5	6	7	8
VI	$C_{23}H_{21}NO_4$ 375.41	heptane 188-190	89	73.10 73.29	5.29 5.55	3.87 3.70	7.52 (m, 1H, H_{arom}), 7.38-7.11 (m, 7H, H_{arom}), 4.75 (m, 3H, C4-H, C-C$\underline{H}_2$-O), 3.73 (s, 3H, OCH_3), 3.51-3.22 (m, 3H, C2-H, C3-H, C2'-H), 3.11-3.00 (2*dd, 1H 2.36-2.19 (m, 2H, } C1'-H, 2.10 (m, 1H, } C3'-H
VII	$C_{25}H_{28}N_2O_4$ 420.49	hexane 143-145	59	71.40 70.71	6.71 6.71	6.66 6.73	7.60 (m, 1H, H_{arom}), 7.40-7.14 (m, 7H, H_{arom}), 5.13 (dd, J_1=11.8 Hz, J_2=2.2 Hz, 1H, H_a z CH_2OH), 4.97 (d, J=11.8 Hz, 1H, H_b z CH_2OH), 4.77 (d, J=3.2 Hz, 1H, C4-H), 3.43-3.15 (m, 5H, C2'-H, C2-H, C3-H, C1'-H), 2.66 (m, 1H, C4'-H), 2.15 (m, 1H, C3'-H), 1.95 (m, 1H, C3'-H), 1.03 s, } 3H, CH_3), 1.00 s, } 3H, CH_3).
VIII	$C_{26}H_{30}N_2O_4$ 434.52	hexane 149-151	82	71.86 71.84	6.96 6.92	6.45 6.30	7.60 (m, 1H, H_{arom}), 7.40-7.14 (m, 7H, H_{arom}), 5.13 (dd, J_1=11.4 Hz, J_2=4 Hz, 1H, H_a z CH_2OH), 4.97 (d, J=12.0 Hz, 1H, H_b z CH_2OH), 4.77 (d, J=3.0 Hz, 1H, C4-H), 3.42-3.06 (m, 5H, C2'-H, C2-H, C3-H, C1'-H), 2.14 (m, 1H, C3'-H), 1.85 (m, 1H, C3'-H), 1.04 (s, 9H, 3·CH_3).

1	2	3	4	5	6	7	8
IX	$C_{27}H_{31}N_3O_4$ $_*0.5\ H_2O$ 470.55	hexane 165-168	80	68.91 69.19	6.85 7.05	8.93 8.60	7.60 (m, 1H, H_{arom}), 7.39-7.13 (m, 7H, H_{arom}), 5.13 (d, J=11.6 Hz, 1H, H_a z CH_2OH), 4.96 (d, J=11.6 Hz, 1H, H_b z CH_2OH), 4.76 (d, J=3 Hz, 1H, C4-H), 3.43-3.16 (m, 5H, C2'-H, C2-H, C3-H, C1'-H), 2.40 (m, 8H, piperazine-H), 2.27 (s, 3H, N-CH_3), 2.00 (m, 1H, C3'-H), 1.79 (dd, J_1=12.8 Hz, J_2=3.4 Hz, 1H, C3'-H)
X	$C_{26}H_{30}N_2O_4$ 434.52	hexane 40-42	83	71.86 71.41	6.96 7.18	6.45 6.40	7.58 (m, 1H, H_{arom}), 7.40-7.12 (m, 7H, H_{arom}), 5.15 (d, J=11.8 Hz, 1H, H_a z CH_2OH), 4.97 (d, J=12 Hz, 1H, H_b z CH_2OH), 4.76 (d, J=3 Hz, 1H, C4-H), 3.42-3.09 (m, 5H, C2'-H, C2-H, C3-H, C1'-H), 2.42 (m, 4H, N-C$\underline{H_2}$-CH_3), 2.10-1.84 (m, 2H, C3'-H), 0.92 (m, 6H, 2· -CH_2-C$\underline{H_3}$).
XI	$C_{24}H_{26}N_2O_4$ 406.46	hexane 168-170	76	70.91 70.46	6.45 6.60	6.89 6.58	7.60 (m, 1H, H_{arom}), 7.39-7.12 (m, 7H, H_{arom}), 5.13 (d, J=11.6 Hz, 1H, H_a z CH_2OH), 4.95 (d, J=11.6 Hz, 1H, H_b z CH_2OH), 4.76 (d, J=3 Hz, 1H, C4-H), 3.42-3.13 (m, 5H, C2'-H, C2-H, C3-H, C1'-H), 2.14 (s, 6H, $N(CH_3)_2$), 2.00 (m, 1H, C3'-H), 1.72 (dd, J_1=12.4 Hz, J_2=3.4 Hz, 1H, C3'-H)

1	2	3	4	5	6	7	8
XII	$C_{26}H_{30}N_2O_4$ 434.52	hexane 132-134	47	71.86 71.97	6.96 7.05	6.45 6.38	8.82, 7.91 (br.s, 1H, NH), 7.51-7.47 (m, 1H, H_{arom}), 7.35-7.05 (m, 7H, H_{arom}), 4.69 (m, 4H, C-C$\underline{H_2}$-O, C4-H, C2'-H), 3.68 (m, 3H, OCH_3), 3.47-3.13 (m, 4H, C2-H, C3-H, C1'-H), 2.03 (m, 2H, C3'-H), 1.40 (m, 7H, 2$_*$-CH_3)
XIII	$C_{27}H_{32}N_2O_4$ 448.55	hexane 150-153	62	72.29 72.12	6.25 6.19	7.19 7.18	7.52 (m, 1H, H_{arom}), 7.37-7.11 (m, 7H, H_{arom}), 4.75 (m, 3H, C4-H, C1-H), 3.728 2 singlets, -OCH_3 3.724 (2 izomers) 3.31 (m, 3H, C1'-H, C2'-H), 3.10 (m, 2H, C3'-H), 2.14 (m, 1H, C2-H), 1.85 (m, 1H, C3-H), 1.03 (s, 9H, 3$_*$ CH_3).
XIV	$C_{28}H_{33}N_3O_4$ 475.57	hexane 156-159	53	70.71 70.71	6.99 7.08	8.84 8.76	7.52 (m, 1H, H_{arom}), 7.37-7.12 (m, 7H, H_{arom}), 4.76 (m, 3H, C4-H, C1-H), 3.73 (s, 3H, -OCH_3), 3.26 (m, 5H, C1'-H, C2'-H, C3'-H), 2.37 (m, 8H, piperazine-H), 2.27 (s, 3H, N-CH_3), 2.00 (m, 1H, C2-H), 1.82 (m, 1H, C3-H).

1	2	3	4	5	6	7	8
XV	$C_{27}H_{320}N_2O_4$ 448.55	hexane 131-134	60	72.29 71.96	6.25 6.00	7.19 6.93	7.52 (m, 1H, H_{arom}), 7.37-7.11 (m, 7H, H_{arom}), 4.76 (m, 3H, C4-H, C1-H), 3.73 (s, 3H, -OCH_3), 3.40-3.07 (m, 5H, C1'-H, C2'-H, C3'-H), 2.41 (m, 4H, 2*-CH_2-CH_3), 2.11-1.82 (m, 2H, C2-H, C3-H), 0.95 (t, 6H, 2*CH_3)
XVI	$C_{25}H_{28}N_2O_4$ 420.51	hexane 156-158	45	71.40 71.25	6.71 6.68	6.68 6.49	7.52 (m, 1H, H_{arom}), 7.37-7.11 (m, 7H, H_{arom}), 4.76 (m, 3H, C4-H, C1-H), 3.73 (s, 3H, -OCH_3), 3.40-3.12 (m, 5H, C1'-H, C2'-H, C3'-H), 2.145 (s, 3H, N-CH_3), 2.412 (s, 3H, N-CH_3), 2.00 (m, 1H, C2-H), 1.72 (m, 1H, C3-H).

2. EXPERIMENTAL

Melting points were determined in a capillary Kofler's apparatus and uncorrected. IR spectra (KBr) were recorded on Specord 75 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian UNITYplus-200 spectrometer. The results of elemental analysis (C, H, N) were within 0.5% of theoretical values (Table). The IR spectra of the compounds showed absorption bands in the range from 1685 cm^{-1} to 1698 cm^{-1} indicating the presence of multiple C=O groups.

1-Hydroxymethyl-dibenzo[e.h]bicyclo[2.2.2]-octane-2,3-dicarboximide III
A mixture of 9-anthracenemethanol (10 g, 0.048 mol), maleimide (4.8 g, 0.048 mol) and toluene (50 ml) was refluxed for 2 h. The solvents were evaporated. The residue was crystallized from ethyl acetate to give compound **III**.

1-Methoxymethyl-dibenzo[e.h]bicyclo[2.2.2]-octane-2,3-dicarboximide IV
A mixture of 9-methoxymethylanthracene (9.3 g, 0.042 mol), maleimide (4.1 g, 0.042 mol) and toluene (50 ml) were refluxed for 2 h. The solvents were evaporated. The residue was crystallized from ethyl acetate to give compound **IV**.

N-(2,3-epoxypropyl)-1-hydroxymethyl- and 1-methoxy-methyldibenzo [e.h]-bicyclo[2.2.2]octane-2,3-dicarboximide V, VI
A mixture of imide **III** (4.0 g, 0.013 mol), K_2CO_3 (1.8 g, 0.013 mol) or imide **IV** (2.3 g, 0.0072 mol), K_2CO_3 (1.0 g, 0.0072 mol) and 1-bromo-2,3-epoxypropane (50 ml) was refluxed for 40 h. Then the inorganic salt was filtered off and the solvent was evaporated. Compounds **V** and **VI** were crystallized from heptane.

General method of preparing of *N*-(3-aminohydroxypropyl) derivatives VII-XVI
A mixture of epoxypropylimide **V** (0.5 g, 0.011 mol) or **VI** (0.4 g, 0.011 mol) and 0.007 mol (for compounds **VII-XI**) or 0.0052 mol (for compounds **XII-XVI**) of an appropriate amine, 40 ml of methanol and five drops of water was refluxed for 54-62 h. The solvent and the excess of amine were distilled off and the precipitate was filtered off and crystallized from hexane to give compounds **VII-XVI**.

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CURRICULA VITAE

Professor Jerzy Kossakowski was born in 1943. He studied chemistry at Warsaw University. In 1967 he obtained M.Sc. title, and started to work as scientific assistant in the Chair and Department of General Chemistry, the Medical University in Warsaw.

In 1975 he presented the thesis "Synthesis of new derivatives of isovisnagine and khellin with an expected pharmacological activity" and obtained the Ph.D. in pharmacy. Synthesis in the field of new derivatives of coumarins, benzofurans and benzopirans resulted in many papers and habilitation "Searching for new compounds affecting the circulation system – in the group of derivatives of furobenzopiranone, benzofuran and benzopiranone" presented in 1989. In April 1993 was appointed to an Assistant Professor post on the Ist Faculty of Medicine, the Medical University of Warsaw.

Scientific activity of Professor comprises investigation of relationships between pharmacological activity and chemical structure of anxiolytics, antidepressants and ß-blockers. Professor's scientific output consists of 60 papers, 7 patents and 83 communications.

Professor Kossakowski is a member of the Polish Pharmaceutical Society.

Monika Jarocka-Wierzba was born in Ciechanowiec in 1972. In 1991 she graduated from secondary school in Ciechanowiec. In the same year she begun studies at Studium Medyczne in Warsaw. She graduated from this school in 1993. In 1994 she began studies in the Chemistry Department of Warsaw University. In 1999 she obtained the degree of Master in Chemistry. Since 1999 she worked in the Chair and Department of Medical Chemistry, The Medical University of Warsaw. Fields of interest: organic synthesis, synthesis of anxiolytic antidepressive and β-adrenolytic compounds. In 2002 she obtained a Ph.D. in Pharmacology Science. During the time she was a co-author of 3 publications and 8 posters.